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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.
09/518,190	03/02/00	HESKETH J	0623.0820001

EXAMINER	
LANDSMAN, R	
ART UNIT	**PAPER NUMBER**
1647	//

HM12/1029
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DATE MAILED: 10/29/01

Please find below and/or attached an Office communication concerning this application or proceeding.

Commissioner of Patents and Trademarks

Office Action Summary	Application No.	Applicant(s)	
	09/518,190	HESKETH ET AL.	
	Examiner	Art Unit	
	Robert Landsman	1647	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *23 August 2001* .

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *9-16 and 21* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *9-16 and 21* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

11)☐ The proposed drawing correction filed on _____ is: a)☐ approved b)☐ disapproved by the Examiner.

If approved, corrected drawings are required in reply to this Office action.

12)☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. §§ 119 and 120

13)☒ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☒ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____ .

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

14)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. § 119(e) (to a provisional application).

a) ☐ The translation of the foreign language provisional application has been received.

15)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449) Paper No(s) _____ .
4) ☐ Interview Summary (PTO-413) Paper No(s). _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: .

DETAILED ACTION

1. Formal Matters

A. Claims 9-22 were pending in the application. Claims 17-20 and 22 were cancelled. Therefore, claims 9-16 and 21 are currently pending.

B. All Statues under 35 USC not found in this Office Action can be found, cited in full, in a previous Office Action.

2. Election/Restriction

A. Restriction to one of the following inventions is required under 35 U.S.C. 121:

I. Claims 9-16 and 21, in part, drawn to a nucleic acid, vector, host cell, method of making a protein, and a chimeric protein, classified in class 435, subclass 69.1.

II. Claims 9 and 15, in part, drawn to a nucleic acid and a non-human animal cell, classified in class 800, subclass 8.

B. The inventions are distinct, each from each other because of the following reasons:

Inventions I and II are independent and distinct, each from the other, because the methods are practiced with materially different process steps for materially different purposes and each method requires a non-coextensive search because of different starting materials, process steps and goals. The methods of making a cell using cell culture techniques are different than those used to produce transgenic animals.

Because these inventions are distinct for the reasons given above and have acquired a separate status in the art as shown by their different classification and recognized divergent subject matter as defined by MPEP § 808.02, the Examiner has *prima facie* shown a serious burden of search (see MPEP § 803). Therefore, an initial requirement of restriction for examination purposes as indicated is proper.

Applicant is advised that the reply to this requirement to be complete must include an election of the invention to be examined even though the requirement be traversed (37 CFR 1.143).

Applicant is reminded that upon cancellation of claims to a non-elected invention, the inventorship must be amended in compliance with 37 CFR § 1.48(b) if one or more of the currently named inventors is no longer an inventor of at least one claim remaining in the application. Any amendment of inventorship must be accompanied by a diligently-filed petition under 37 CFR § 1.48(b) and by the fee required under 37 CFR § 1.17 (h).

Maintained Objections

A. The objection to the title as not being descriptive is maintained since Applicants did not address this issue. This matter will be handled if this case is found to have allowable subject matter. For example, "Expression system for the secretion of intracellular proteins."

Withdrawn Claim Rejections

1. Claim Rejections - 35 USC § 112, first paragraph

A. All rejections under 35 USC 112, first paragraph, have been withdrawn in view of Applicants' arguments that one of ordinary skill in the art would know whether the 3'UTR has been sufficiently disrupted to negate its intracellular targeting effects.

2. Claim Rejections - 35 USC § 112, second paragraph

A. All rejections under 35 USC 112, second paragraph, have been withdrawn in view of Applicants' arguments, amendments, or cancellation of the claims.

3. Claim Rejections - 35 USC § 103

A. All rejections under 35 USC 103 have been withdrawn since Applicants argue that the protein of Lee et al. since the mRNA encoding this protein is naturally targeted to the ER. However, a new rejection under 35 USC 103 is presented below.

New Claim Rejections

1. Claim Rejections - 35 USC § 112, second paragraph

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

A. Claim 16 is rejected under 35 U.S.C. 112, second paragraph, as being incomplete for omitting essential steps, such omission amounting to a gap between the steps. See MPEP § 2172.01. The omitted steps is: purifying the protein.

2. Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

A. Claims 9-16 are rejected under 35 U.S.C. 103(a) as being unpatentable over Lee et al. (Reference AT5 on the Form PTO-1449) in view of Kordula et al. (Biochem J. 293:187-193, 1993) and further in view of Maeda et al. (Reference AS6 on the Form PTO-1449). The claims recite a nucleic acid molecule encoding a mammalian signal peptide from a protein normally secreted from a mammalian cell linked to a

nucleic acid not normally secreted from a mammalian cell, wherein the 3'-UTR has been altered in order to affect intracellular localization of the nucleic acid. The claims also recite vectors, mammalian cells and methods of making the protein. Lee et al. teach an expression-secretion vector for mammalian cells in which the vector contains a signal peptide from mouse IgM (mammal) and a cDNA of sialyltransferase (Abstract and Materials and Methods). This vector was then transfected into mammalian COS-7 cells and the produced protein was purified (Abstract and Materials and Methods). However, since this protein is a membrane-bound protein, it is synthesized on membrane-bound polysomes.

Lee et al. do not teach a nucleic acid molecule comprising a nucleic acid of a protein not normally secreted from a mammalian cell. However, Kordula et al. do teach the molecular cloning and expression of an intracellular protein, serpin which would not be expected to be targeted to the ER or membrane-bound polysomes (Abstract and page 188, right column, 4th paragraph). The full-length cDNA of serpin is 2.3 kb, which includes 939 bases of 3'-UTR (paragraph 1 under "Results" and first full paragraph on page 192). However, Kordula et al. also teach the 1.3 kb *NcoI-HindIII* fragment containing only the entire coding sequence of HLEI (i.e. without the 3'-UTR). They also teach the placement of this coding region into a vector for expression (page 188, right column, 4th paragraph). Kordula et al. do not specifically teach RNA. However, one of ordinary skill in the art would immediately envision the RNA sequence given the DNA sequence of the coding region of Kordula et al.

Therefore, it would have been obvious to one of ordinary skill in the art to have used the invention of Kordula et al., who teach a coding sequences of HLEI, a protein not normally secreted from mammalian cells, which has a deleted, or, at most, altered 3'-UTR, in the invention of Lee et al., who teach a nucleic acid molecule of a protein which is not normally secreted by a cell (sialyltransferase) fused to a mammalian signal sequence, as well as vectors and host cells comprising these nucleic acids. One of ordinary skill in the art would have been motivated to combine these methods in order to be able

to produce secreted proteins which are not normally secreted by a cell in order to obtain larger quantities of the protein for purification and potential medical use.

Neither Lee et al. or Kordula et al. teach the signal peptide from albumin as recited in claim 13. However, Maeda et al. do teach the use of the signal peptide from albumin in order to express large quantities of protein (Abstract). It would have been obvious to one of ordinary skill in the art to have substituted the albumin signal sequence of Maeda et al. for the signal peptide of Lee et al. for the purpose of producing a fusion protein which can be secreted since it was well-known at the time of the invention that albumin is secreted from mammalian cells and that the use of albumin signal sequence is capable of generating large (even "mass") quantities of secreted protein (see Conclusion).

Therefore, it would have been obvious to the artisan at the time of the invention to have substituted the coding sequence of Kordula et al. and the albumin signal sequence of Maeda et al. for the cDNA sequence and mouse IgM signal peptide of Lee et al. in order to produce an intracellular protein which is able to be secreted in order to obtain larger quantities of the protein for purification and potential medical use. The artisan would have been motivated to use the signal sequence from albumin since this sequence has been shown to generate large (even "mass") quantities of secreted protein, as would be desired from the artisan.

B. Claim 21 is rejected under 35 U.S.C. 103(a) as being unpatentable over Lee et al. (Reference AT5 on the Form PTO-1449) in view of Kordula et al. (Biochem J. 293:187-193, 1993) and further in view of Smith and Johnson (Gene 67:31-40, 1988). The claim recites a chimeric protein produced by expressing a nucleic acid molecule encoding a mammalian signal peptide from a protein normally secreted from a mammalian cell linked to a nucleic acid not normally secreted from a mammalian cell, wherein the 3'-UTR has been altered in order to affect intracellular localization of the nucleic acid.

The teachings of Lee et al. and Kordula et al. are taught in the above rejection under 35 USC 103.

Neither Lee et al. or Kordula et al. teach a chimeric protein encoded for by the claimed nucleic acid. However, Smith and Johnson do teach chimeric proteins comprising a gene to be expressed, fused to a glutathione S-transferase gene (GST; Summary and Materials and Methods). It would have been obvious to one of ordinary skill in the art to have substituted the cDNA encoding GST in frame with the coding region of Kordula et al. for the purpose of producing a chimeric (fusion) protein which can then be used to produce a protein which would be easier to purify to homogeneity than that of Kordula et al. in the absence of GST. It would have been obvious to the artisan at the time of the invention to have used the DNA encoding GST, as taught by Smith and Johnson, in frame with the coding region of the non-secreted protein of Kordula et al., in the invention of Lee et al. since as was well-known in the art at the time of the invention, GST can, and has been, used in the field to produce proteins which are more pure than those same proteins which are not fused to GST. In addition, Smith and Johnson teach that, as of 1988, GST fusion proteins have been used successfully for the purification of more than 30 different polypeptides (Abstract). The artisan would have been further motivated to use GST, which uses affinity-chromatography and does not denature proteins, since the use of denaturing reagents to purify protein can alter the antigenicity and functional activity of the purified product, or, as in certain systems, the binding of fusion proteins to IgG complicates immunological analysis (page 32 of Smith and Johnson, left column, first paragraph).

In summary, it would have been obvious to one of ordinary skill in the art to have substituted the cDNA encoding GST, as taught by Smith and Johnson, in frame with the coding region of Kordula et al., in the method of Lee et al. for the purpose of producing a chimeric (fusion) protein which can then be used to produce proteins which are purer and functional than those same proteins which are not fused to GST.

Advisory information

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Robert Landsman whose telephone number is (703) 306-3407. The examiner can normally be reached on Monday - Friday from 8:00 AM to 5:00 PM (Eastern time) and alternate Fridays from 8:00 AM to 5:00 PM (Eastern time).

If attempts to reach the examiner by telephone are unsuccessful, the Examiner's supervisor, Gary Kunz, can be reached on (703) 308-4623.

Official papers filed by fax should be directed to (703) 308-4242. Fax draft or informal communications with the examiner should be directed to (703) 308-0294.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the Group receptionist whose telephone number is (703) 308-0196.

Robert Landsman, Ph.D.
Patent Examiner
Group 1600
October 25, 2001

Gary L. Kunz

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